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10/532,681	02/20/2007	Sergei Anatolievich Lukyanov	U 015745-9	6233

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,681	LUKYANOV ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-11,13-17 and 27-30* is/are pending in the application.

4a) Of the above claim(s) *9-11 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-8,13,17 and 27-30* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/26/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice of sequence compliance*.

DETAILED ACTION

This application 10/532,681 is a 371 of PCT/RU03/00474 filed on 11/05/2003 which claims benefit of 60/425,570 filed on 11/12/2002, and claims benefit of 60/429,795 filed on 11/27/2002, and claims benefit of 60/464,258 filed on 04/21/2003, and claims benefit of 60/480,080 filed on 06/20/2003.

Election/Restriction

Applicant's election with traverse of Group I, claims 1-6, 12, 13, 17, and 18, drawn to **(i)** An isolated nucleic acid molecule comprising nucleotide sequences, which encodes a fluorescent protein having at least 85% identity with an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 10, 12, 14, 16, 18, 20, and 22 (amended claim 1 filed on 10/27/2008); **(ii)** A vector comprising the nucleic acid molecule according to claim 1 (claim 5), and **(iii)** An expression cassette comprising (a) a transcriptional initiation region that is functional in an expression host; (b) the nucleic acid molecule according to claim 1; and (c) and a transcriptional termination region functional in said expression host (amended claim 6 filed on 10/27/2008), in the reply filed on 10/27/2008 is acknowledged. With regard to further restriction of recited SEQ ID Nos, Applicant elected the amino acid sequence of SEQ ID No. 10 which corresponds to the nucleic acids of SEQ ID No. 9 (See supplemental response filed on 11/07/2008). The traversal is on the ground(s) that **(i)** SEQ IDs 2, 4, 6, 10, 18, 20 represent products of unrelated structure and function, the identified SEQ IDs represent initial natural protein (SEQ ID NO: 2) and its mutants with few sequence modifications. All the identified SEQ IDs have GFP-like domain contributing in fluorescent properties with regions of **high homology**

over the amino acid sequences and are significantly different from other known florescent proteins (sequence identity is less than 55% and characteristic gap profile is present). In view of the above the Applicant submits that the claimed SEQ IDs 2, 4, 6, 10, 18, 20 have a common core structure sufficient to meet applicable PCT requirements; **(ii)** Regarding the restriction of Groups I and II, Applicants argues that identification of these groups as nucleic acids and host cells alone fails to establish a lack of technical interrelationship of corresponding special technical features; **(iii)** Regarding the restriction of Groups I and V, Applicants argues that the restriction between Groups 1 and V is improper and requests withdrawal thereof because these Groups relate to the nucleic acid and method of its use in a recombinant DNA technique for making a protein or polypeptide encoded by a nucleic acid molecule of claim 1.

The traversal is not found persuasive because as stated in the Restriction requirement mailed on 09/25/2008 **(i)** Each nucleic acid molecule encodes a distinct fluorescent protein, which is distinct in structure and function, and requires different processes of excitation and emission for detection. The sequences do not meet the criteria of requirements according to the guidelines in Section (f)(i)(a) of Annex B of the PCT Administrative Instructions, as they do not share, one with another, a common core structure, despite of asserted high homology (i.e. less than 55%), especially in light of recitation of "at least 85% identity" that encompasses up to 15% non-identical sequences located anywhere within any segment of a given SEQ ID No. Accordingly, unity of invention between the nucleic acid (and corresponding amino acid) sequences of the instant application is lacking and each nucleic acid sequence claimed is considered to constitute a special technical feature; Therefore, <u>further restriction to a given SEQ ID No of nucleic acid which corresponds to a given SEQ ID No of amino acid is maintained</u>; For

(ii), upon further consideration, the restriction between non-elected Group II (claims 7 and 8) and elected Group I is *withdrawn*; For **(iii),** As stated in the Restriction requirement mailed on 09/25/2008, Applicant's claims encompass multiple inventions, multiple products (nucleic acid, protein, antibody, transgenic plant, transgenic animal) and multiple methods (methods of making and methods of using the products), and do not have a special technical feature which link the inventions one to the other, and lack unity of invention. Furthermore, there is no common technical feature in all groups. Additionally, as stated in the Restriction requirement mailed on 09/25/2008 under section titled MPEP 1893.03(d) Unity of Invention Rejoinder, MPEP 1893.03(d) states: If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. Any nonelected product claim that requires all the limitations of an allowable product claim, and any nonelected process claim that requires all the limitations of an allowable process claim, should be rejoined. See MPEP § 821.04 and § 821.04(a). Any nonelected processes of making (and/or using) an allowable product should be considered for rejoinder following the practice set forth in MPEP § 821.04(b). Therefore, the restriction between non-elected Group V (claim 11) pertaining to making of elected invention Group I is maintained, and claim 11 remains as a withdrawn claim.

In the claim set filed on 10/27/2008, claims 2-4, 12, and 18-26 are cancelled. Claims 27-30 are newly added, which are assigned to the elected invention Group I. Accordingly, claims 1, 5-11, 13-17, and 27-30 are pending. Claims 9-11 and 14-16 are withdrawn from further

consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 5-8, 13, 17, and 27-30 are currently under examination to the extent of elected SEQ ID NO: 9 (705 nucleotides) that corresponds to elected SEQ ID No. 10 (234 amino acid residues). Applicant is advised to amend the claim identifiers of claims 11, and 13 in reply to this office action.

The requirement is still deemed proper and is therefore made FINAL.

Priority

It is noted that provisional applications 60/429,795 filed on 11/27/2002, 60/464,258 filed on 04/21/2003, and 60/480,080 filed on 06/20/2003, did not disclose either SEQ ID No: 10 or SEQ ID No: 9. The provisional application 60/425,570 filed on 11/12/2002 discloses SEQ ID No 2 that is identical to the SEQ ID No: 10 of instant application, but 60/425,570 filed on 11/12/2002 did not disclose SEQ ID No.9 of instant application since SEQ ID No. 1 and SEQ ID No. 3 disclosed in 60/425,570 are not the same as SEQ IN No. 9 of instant application

Therefore, the priority date of claim 1, which recites SEQ ID No. 10 and its dependent claims 5-8, 13, 17, 27, 28, and 29 (which is interpreted as a dependent claim of claim 1, see 112 second below) is determined to be 11/12/2002, the filing date of provisional application 60/425,570. The priority date of claim 30, which recites SEQ ID No. 9, is determined to be 11/05/2003, the filing date of PCT/RU03/00474.

Sequence compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The alignment of the sequences listed in Figure 1 requires a sequence identifier. See MPEP 1.821.** Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing."

Applicant is encouraged to identify any other such sequences that may also require sequence identifiers throughout the specification.

Claim Objection

1. Claims 1, 28 and 30 are objected to for being drawn to a non-elected invention. Specifically, Applicants have elected SEQ ID No. 10, which is encoded by SEQ ID No. 9 as elected invention recited in claims 1, 28, and 30 and as such, claim 1 and dependent claims 5, 6, 13, 17, 27, 28, and 30 are examined only to the extent that they read on a SEQ ID No. 10, which is encoded by SEQ ID No. 9. Applicants are required to delete the non-elected subject matter from the instant claims 1, 28, and 30.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 reads as follows: A isolated nucleic acid that hybridizes under stringent conditions to the nucleic acid of claim 26, wherein said nucleic acid encodes a fluorescent protein. However, claim 26 is cancelled.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

3. Claims 1, 5-8, 13, 17, and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an isolated nucleic acid molecule comprising nucleotide sequences, which encodes a fluorescent protein having at least 85% identity with an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, **10**, 12, 14, 16, 18, 20, and 22 (claims 1, 13, and 27-30), a vector and an expression vector comprising the nucleic acid of

claim 1 (claims 5 and 6), a cell comprising the nucleic acid of claim 1 (claims 7 and 8), a kit comprising the nucleic acid of claim 1 (claim 17).

The specification discloses SEQ ID No. 10 (a 234-amino acid long polypeptide) is a humanized version of the phiYFG-M1, which is a mutant form of phiYFP generated by random mutagenesis of phiYFP (an YFP isolated from microorganism *Philalidium* sp.). The specification discloses that SEQ ID No. 9 (a 705-nucleotide long polynucleotide) encodes SEQ ID No. 10. The specification discloses the alignment between GFP (from jelly fish), phiYFP, hydriGFP, and hm2CP in Figure 1. The phiYFP shares only ~50% identity with well characterized GFP (from jelly fish) (See Figure 1 disclosed in specification as well as alignments provided in this office action under 102 rejections below).

Based on sequence search performed by the Examiner, it is noted that SEQ ID No. 10 (phiYFG-M1) shares 96% identity with phiYFP (an YFP isolated from microorganism *Philalidium* sp.), see alignment below.

```
RESULT 1
Q6RYS7_9CNID
ID   Q6RYS7_9CNID            Unreviewed;       234 AA.
AC   Q6RYS7;
DT   05-JUL-2004, integrated into UniProtKB/TrEMBL.
DT   05-JUL-2004, sequence version 1.
DT   24-JUL-2007, entry version 13.
DE   Yellow fluorescent protein.
OS   Phialidium sp. SL-2003.
OC   Eukaryota; Metazoa; Cnidaria; Hydrozoa; Hydroida; Leptomedusae;
OC   Campanulariidae; Phialidium.
OX   NCBI_TaxID=258839;
RN   [1]
RP   NUCLEOTIDE SEQUENCE.
RX   PubMed=14963095; DOI=10.1093/molbev/msh079;
RA   Shagin D.A., Barsova E.V., Yanushevich Y.G., Fradkov A.F.,
RA   Lukyanov K.A., Labas Y.A., Semenova T.N., Ugalde J.A., Meyers A.,
RA   Nunez J.M., Widder E.A., Lukyanov S.A., Matz M.V.;
RT   "GFP-like proteins as ubiquitous metazoan superfamily: evolution of
RT   functional features and structural complexity.";
RL   Mol. Biol. Evol. 21:841-850(2004).
CC   ---------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ---------------------------------------------------------------------
DR   EMBL; AY485333; AAR85349.1; -; mRNA.
DR   HSSP; P42212; 1B9C.
DR   GO; GO:0008218; P:bioluminescence; IEA:InterPro.
DR   GO; GO:0006091; P:generation of precursor metabolites and energy; IEA:InterPro.
DR   GO; GO:0018298; P:protein-chromophore linkage; IEA:InterPro.
DR   InterPro; IPR011584; GFP_related.
DR   InterPro; IPR000786; Green_fl_protein.
DR   Pfam; PF01353; GFP; 1.
DR   PRINTS; PR01229; GFLUORESCENT.
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DR   ProDom; PD013756; Green_fl_protein; 1.
PE   2: Evidence at transcript level;
SQ   SEQUENCE   234 AA;  26051 MW;  0E7F2DEAAE735D9A CRC64;

  Query Match             96.0%;  Score 1231;  DB 2;  Length 234;
  Best Local Similarity   96.6%;  Pred. No. 1.2e-102;
  Matches  226;  Conservative    3;  Mismatches    5;  Indels    0;  Gaps    0;

Qy          1 MSSGALLFHGKIPYVVEMEGNVDGHTFSIRGKGYGDASVGKVDAQFICTTGDVPVPWSTL 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MSSGALLFHGKIPYVVEMEGNVDGHTFSIRGKGYGDASVGKVDAQFICTTGDVPVPWSTL 60

Qy         61 VTTLTYGAQCFAKYGPELKDFYKSCMPDGYVQERTITFEGDGNFKTRAEVTFENGSVYNR 120
              ||||||||||||||||||||||||||:|||||||||||||| ||||||||||||||||
Db         61 VTTLTYGAQCFAKYGPELKDFYKSCMPEGYVQERTITFEGDGVFKTRAEVTFENGSVYNR 120

Qy        121 VKLNGQGFKKDGHVLGKNLEFNFTPHCLYIWGDQANHGLKSAFKICHEITGSKGDFIVAD 180
              |||||||||||||||||||||||||||||||||||||||||||| ||||||| ||||||
Db        121 VKLNGQGFKKDGHVLGKNLEFNFTPHCLYIWGDQANHGLKSAFKIMHEITGSKEDFIVAD 180

Qy        181 HTQMNTPIGGGPVHVPEYHHMSYHVKLSKDVTDHRDNMSLKETVRAVDCRKTYL 234
              ||||||||||||||||||::||| |||||||||||||| ||||||||||||
Db        181 HTQMNTPIGGGPVHVPEYHHITYHVTLSKDVTDHRDNMSLVETVRAVDCRKTYL 234
```

The specification does not provide any information regarding the structure-function correlation of phiYFP in terms which amino acids are necessary and sufficient for phiYFP to be a fluorescent protein. The nucleotide sequences that encodes a fluorescent protein with at least 85% identity with SEQ ID No. 10, variants, and fragments thereof encompassed within the genus of nucleotide molecules encodes 85% fluorescent protein with at least 85% identity with SEQ ID No. 10, have not been disclosed. The specification discloses isolation of polynucleotide SEQ ID No. 9 encoding polypeptide SEQ ID No. 10 by random mutagenesis. There is no evidence on the record of a relationship between the structure of any nucleic acid encoding a fluorescent protein and the claimed nucleic acid molecules encodes a fluorescent protein with at least 85% identity with SEQ ID No. 10, over the entire length of SEQ ID No: 10, that would provide any reliable information about the structure of other nucleic acid encoding a fluorescent protein within the genus. In the absence of a functional assay it would not be possible to test variants of the claimed sequences for biological activity. Also with regard to the allelic variants encompassed by the claims, the skilled artisan cannot envision the structure of such a variant because such variants are randomly produced in nature, and cannot be predicted from a known

sequence. The specification does not teach any characteristics of an "allelic" variant that would distinguish it from a non-natural variant constructed by the hand of man. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes at sequence level possessed by member of the genus. Consequently, since Applicant was in possession of only the nucleotide sequences SEQ ID No.10 encoded by SEQ ID No. 9 and since the art recognized variation among the species of the genus of nucleic acid molecules encodes a fluorescent protein with at least 85% identity with SEQ ID No. 10, the SEQ ID No. 9 encoding SEQ ID No. 10 was not representative of the claimed genus. This is because the amino acids that are necessary and sufficient for phiYFP to be a fluorescent protein have not been disclosed and SEQ ID SEQ ID No. 9 encoding SEQ ID No. 10 was obtained by random mutagenesis. Therefore, Applicant was not in possession of the genus of the nucleotide sequences that encodes a fluorescent protein with at least 85% identity with SEQ ID No. 10 over the entire length of SEQ ID No: 10 as encompassed by the claims.

It is further noted that claim 29 (which is interpreted as a dependent claim of claim 1) is directed to the limitation "hybridization under stringent conditions". The specification only discloses an example (a species) of various conditions that Applicant regards as "stringent conditions". The art recognizes that "hybridization under stringent conditions" is determined by variations in multiple factors (detergents, salts, hydrogen bond competitor, and temperatures etc.). Therefore, the genus encompassed by "hybridization under stringent conditions" is not described to render a skilled artisan to possess the sequences by hybridization that encodes a fluorescent protein having at least 85% identity with SEQ ID No. 10. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description

requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Scope of Enablement

4. Claims 1, 5-8, 13, 17, and 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising of SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No. 10, and a vector/cell/kit comprising SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No. 10, **does not** reasonably provide enablement for (1) any isolated nucleic acid molecule encodes a fluorescent protein other than SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No. 10, or (2) any vector/cell/kit comprising any isolated nucleic acid molecule encodes a fluorescent protein other than SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No. 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered

in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The basis of this scope of enablement is hinged on the lack of enabling support on the structure/function relationship to make and use any isolated nucleic acid molecule comprising nucleotide sequences encoding a fluorescent protein having at least 85% identity with SEQ ID No. 10.

The nature of the instant invention is drawn to an isolated nucleic acid molecule comprising nucleotide sequences, which encodes a fluorescent protein having at least 85% identity with an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, **10**, 12, 14, 16, 18, 20, and 22 (claims 1, 13, and 27-30), a vector and an expression vector comprising the nucleic acid of claim 1 (claims 5 and 6), a cell comprising the nucleic acid of claim 1 (claims 7 and 8), a kit comprising the nucleic acid of claim 1 (claim 17).

The breadth of the claims encompasses any isolated nucleic acid molecule encodes a fluorescent protein in addition to SEQ ID No. 9 that encodes a fluorescent protein consisting of SEQ ID No. 10, and any vector/cell/kit comprising any isolated nucleic acid molecule encodes a fluorescent protein in addition to SEQ ID No. 9 encodes a fluorescent protein consisting of SEQ ID No. 10.

The specification discloses SEQ ID No. 10, a 234-amino acid long polypeptide, is a humanized version of the phiYFG-M1, which is a mutant form of phiYFP generated by random

_____ of phiYFP (an YFP isolated from microorganism *Philalidium* sp.). The specification discloses that SEQ ID No. 9 (a 705-nucleotide long polynucleotide) encodes SEQ ID No. 10. The specification discloses the alignment between GFP (from jelly fish), phiYFP, hydriGFP, and hm2CP in Figure 1. The phiYFP shares only about 50% identity with well characterized GFP (from jelly fish) (See Figure 1 disclosed in specification as well as alignments provided in this office action under 102 rejections).

Based on sequence search performed by the Examiner, it is noted that SEQ ID No. 10 (phiYFG-M1) shares 96% identity with phiYFP (an YFP isolated from microorganism *Philalidium* sp.), see alignment in the preceding written description rejection.

The specification does not provide any guidance regarding the structure-function correlation of phiYFP in terms which amino acids are necessary and sufficient for phiYFP to be a fluorescent protein. It would require undue experimentation for an artisan to determine which amino acids are necessary and sufficient for phiYFP-M1 (i.e. the claimed SEQ ID No. 10) to be a fluorescent protein to support the breadth of the claims.

In the art, it is unpredictable how variations of sequences in a given fluorescent protein would affect its function as a fluorescent protein. For instance, **Shagi et al.** teaches that homologs of the green fluorescent protein (GFP), including the recently described GFP-like domains of certain extracellular matrix proteins in Bilaterian organisms, are remarkably similar at the protein structure level, yet they often perform totally unrelated functions, thereby warranting recognition as a superfamily (See Shagin et al., GFP-like proteins as ubiquitous metazoan superfamily: evolution of functional features and structural complexity, *Mol Biol Evol.* 21(5):841-50, 2004).

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 1, 5-8, 13, 17, and 27-30.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1, 5-8, 13, 17, and 27-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Baubet et al. (Baubet et al., US 2008/0213879, publication date 09/04/2008, Division of US 6,936,475, which is a Continuation of PCT/EP01/07057, WO 2001/092300, filed on 06/01/2001).

The following claim interpretations are applied in this rejection.

(i) Claim 1 reads as follows: An isolated nucleic acid molecule comprising nucleotide sequences, which encodes a fluorescent protein having at least 85% identity with an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, **10**, 12, 14, 16, 18, 20, and 22. Claim 1 reads on any isolated nucleic acid molecule comprising nucleotide sequences, which

encodes a fluorescent protein having amino acid sequences that have at least 85% identity of any fragment of SEQ ID No. 10. It is emphasized that the phrase "consisting of SEQ ID NOs: 2, 4, 6, **10**, 12, 14, 16, 18, 20, and 22" is only limiting to one of recited SEQ ID No and does not limit the transitional term "comprising" recited in line 1 of claim 1. In this regard, MPEP 2111.02 states: In determining the scope of applicant's claims directed to "a purified oligonucleotide comprising at least a portion of the nucleotide sequence of SEQ ID NO:1 wherein said portion consists of the nucleotide sequence from … to 2473 of SEQ ID NO:1, and wherein said portion of the nucleotide sequence of SEQ ID NO:1 has promoter activity," the court stated that the use of "consists" in the body of the claims did not limit the open-ended "comprising" language in the claims (emphases added). *Id.* at 1257, 73 USPQ2d at 1367.

(ii) Claim 13 reads as follows: A nucleic acid molecule having a sequence that is substantially the same as, or identical to a nucleotide sequence of at least 300 residues in length of the nucleic acid molecule according to claim 1. The limitation "at least 300 residues in length of the nucleic acid molecule" reads on those identical sequences that are not necessarily continuous.

(iii) Claim 29 is interpreted as a dependent claim of claim 1, rather than a dependent claim of claim 26, which is cancelled.

With regard to claims 1, 5-8, 13, and 27-30, Baubet et al. teaches a modified bioluminescent system comprising a fluorescent molecule covalently linked with a photoprotein, wherein said link between the two proteins has the function to stabilize the modified bioluminescent system and allowing the transfer of the energy by Chemiluminescence Resonance Energy Transfer (CRET) in a host cell (See abstract and Figures 9-11, Bauet et al. US

2008/0213879). Baubet et al. teaches DNA construct with CMV promoter drive the expression of nucleic acid sequences encoding sequences of mutated GFP, followed by the sequences of Poly A of SV40 (See Figure 1, Baubet et al. US 2008/0213879)

With regard to the limitation "kit" recited in claim 17, Baubet et al. teaches kit for measuring the transfer of energy *in vivo* or *in vitro* contains at least one of the polypeptides according to the invention or the polynucleotide according to the invention and the reagents necessary for visualizing or detecting the said transfer in presence or in absence of a molecule of interest (See paragraph [0027], Baubet et al., US 2008/0213879)

The following sequence alignments are SEQ ID No. 10 and SEQ ID No. 9 of instant application aligned with disclosed SEQ ID Nos by Baubet et al. (Baubet et al., US 2008/0213879).

(A) Alignment of SEQ ID No. 10 of instant application with SEQ ID Nos 1-6 of Baubet et al.

```
RESULT 1
US-11-149-177-1 (SEQ ID No. 1)
; Sequence 1, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
;  APPLICANT: BAUBET, VALERIE
;  APPLICANT:LE MOUELLIC, HERVE
;  APPLICANT:BRULET, PHILIPPE
;  TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
;  TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
;  FILE REFERENCE: 03495-0207-00000
;  CURRENT APPLICATION NUMBER: US/11/149,177
;  CURRENT FILING DATE: 2005-06-10
;  PRIOR APPLICATION NUMBER: 09863901
;  PRIOR FILING DATE: 2001-05-24
;  PRIOR APPLICATION NUMBER: 60/208,314
;  PRIOR FILING DATE: 2000-06-01
;  PRIOR APPLICATION NUMBER: 60/210,526
;  PRIOR FILING DATE: 2000-06-06
;  PRIOR APPLICATION NUMBER: 60/255,111
;  PRIOR FILING DATE: 2000-12-14
;  NUMBER OF SEQ ID NOS: 48
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 1
;  LENGTH: 432
;  TYPE: PRT
;  ORGANISM: Aequorea victoria
US-11-149-177-1

  Query Match            50.5%;  Score 648;  DB 4;  Length 432;
  Best Local Similarity  53.9%;  Pred. No. 6.5e-60;
  Matches  123;  Conservative   40;  Mismatches   61;  Indels    4;  Gaps    2;

Qy          1 MSSGALLFHGKIPYVVEMEGNVDGHTFSIRGKGYGDASVGKVDAQFICTTGDVPVPWSTL 60
```

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              || |  || | :| :||::|:|:|| ||: |:| |||: ||:  :|||||| :|||| ||
Db          1 MSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTL 60

Qy         61 VTTLTYGAQCFAKYGPELK--DFYKSCMPDGYVQERTITFEGDGNFKTRAEVTFENGSVY 118
              ||||||| |||::|   :|  ||:|| ||:|||||||| |: |||:|||||| ||  ::
Db         61 VTTLTYGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLV 120

Qy        119 NRVKLNGQGFKKDGHVLGKNLEFNFTPHCLYIWGDQANHGLKSAFKICHEITGSKGDFIV 178
              ||::| |  ||:||::||  ||:|:  | :||  |:  :|:|: ||| | |    |   :
Db        121 NRIELKGIDFKEDGNILGHKLEYNYNSHNVYIMADKQKNGIKANFKIRHNI--EDGSVQL 178

Qy        179 ADHTQMNTPIGGGPVHVPEYHHMSYHVKLSKDVTDHRDNMSLKETVRA 226
              ||| | ||||| ||| :|: |::|    ||||  : ||:| | | | |
Db        179 ADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMVLLEFVTA 226


RESULT 2
US-11-149-177-2 (SEQ ID No. 2)
; Sequence 2, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
;  APPLICANT: BAUBET, VALERIE
;  APPLICANT:LE MOUELLIC, HERVE
;  APPLICANT:BRULET, PHILIPPE
;  TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
;  TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
;  FILE REFERENCE: 03495-0207-00000
;  CURRENT APPLICATION NUMBER: US/11/149,177
;  CURRENT FILING DATE: 2005-06-10
;  PRIOR APPLICATION NUMBER: 09863901
;  PRIOR FILING DATE: 2001-05-24
;  PRIOR APPLICATION NUMBER: 60/208,314
;  PRIOR FILING DATE: 2000-06-01
;  PRIOR APPLICATION NUMBER: 60/210,526
;  PRIOR FILING DATE: 2000-06-06
;  PRIOR APPLICATION NUMBER: 60/255,111
;  PRIOR FILING DATE: 2000-12-14
;  NUMBER OF SEQ ID NOS: 48
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 2
;  LENGTH: 441
;  TYPE: PRT
;  ORGANISM: Aequorea victoria
US-11-149-177-2

  Query Match             50.5%;  Score 648;  DB 4;  Length 441;
  Best Local Similarity   53.9%;  Pred. No. 6.7e-60;
  Matches  123;  Conservative   40;  Mismatches   61;  Indels    4;  Gaps    2;

Qy          1 MSSGALLFHGKIPYVVEMEGNVDGHTFSIRGKGYGDASVGKVDAQFICTTGDVPVPWSTL 60
              || |  || | :| :||::|:|:|| ||: |:| |||: ||:  :|||||| :|||| ||
Db          1 MSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTL 60

Qy         61 VTTLTYGAQCFAKYGPELK--DFYKSCMPDGYVQERTITFEGDGNFKTRAEVTFENGSVY 118
              ||||||| |||::|   :|  ||:|| ||:|||||||| |: |||:|||||| ||  ::
Db         61 VTTLTYGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLV 120

Qy        119 NRVKLNGQGFKKDGHVLGKNLEFNFTPHCLYIWGDQANHGLKSAFKICHEITGSKGDFIV 178
              ||::| |  ||:||::||  ||:|:  | :||  |:  :|:|: ||| | |    |   :
Db        121 NRIELKGIDFKEDGNILGHKLEYNYNSHNVYIMADKQKNGIKANFKIRHNI--EDGSVQL 178

Qy        179 ADHTQMNTPIGGGPVHVPEYHHMSYHVKLSKDVTDHRDNMSLKETVRA 226
              ||| | ||||| ||| :|: |::|    ||||  : ||:| | | | |
Db        179 ADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMVLLEFVTA 226


RESULT 3
US-11-149-177-3 (SEQ ID No. 3)
; Sequence 3, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
;  APPLICANT: BAUBET, VALERIE
;  APPLICANT:LE MOUELLIC, HERVE
;  APPLICANT:BRULET, PHILIPPE
;  TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
;  TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
;  FILE REFERENCE: 03495-0207-00000
;  CURRENT APPLICATION NUMBER: US/11/149,177
;  CURRENT FILING DATE: 2005-06-10
;  PRIOR APPLICATION NUMBER: 09863901
;  PRIOR FILING DATE: 2001-05-24
;  PRIOR APPLICATION NUMBER: 60/208,314
;  PRIOR FILING DATE: 2000-06-01
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;  PRIOR APPLICATION NUMBER: 60/210,526
;  PRIOR FILING DATE: 2000-06-06
;  PRIOR APPLICATION NUMBER: 60/255,111
;  PRIOR FILING DATE: 2000-12-14
;  NUMBER OF SEQ ID NOS: 48
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 3
;  LENGTH: 450
;  TYPE: PRT
;  ORGANISM: Aequorea victoria
US-11-149-177-3

  Query Match             50.5%;  Score 648;  DB 4;  Length 450;
  Best Local Similarity   53.9%;  Pred. No. 6.9e-60;
  Matches  123;  Conservative   40;  Mismatches   61;  Indels    4;  Gaps    2;

Qy          1 MSSGALLFHGKIPYVVEMEGNVDGHTFSIRGKGYGDASVGKVDAQFICTTGDVPVPWSTL 60
              || |  || | :| :||::|:|:|:|| ||: |:| |||: ||:  :|||||| :|||| ||
Db          1 MSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTL 60

Qy         61 VTTLTYGAQCFAKYGPELK--DFYKSCMPDGYVQERTITFEGDGNFKTRAEVTFENGSVY 118
              ||||||| |||::|   :|  ||:|| ||:|||||||| |: |||:|||||| ||  ::
Db         61 VTTLTYGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLV 120

Qy        119 NRVKLNGQGFKKDGHVLGKNLEFNFTPHCLYIWGDQANHGLKSAFKICHEITGSKGDFIV 178
              ||::| |  ||:||::||  ||:|:  | :||  |:  :|:|: ||| | |    |   :
Db        121 NRIELKGIDFKEDGNILGHKLEYNYNSHNVYIMADKQKNGIKANFKIRHNI--EDGSVQL 178

Qy        179 ADHTQMNTPIGGGPVHVPEYHHMSYHVKLSKDVTDHRDNMSLKETVRA 226
              ||| | ||||| ||| :|: |::|    ||||  : ||:| | | | |
Db        179 ADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMVLLEFVTA 226


RESULT 4
US-11-149-177-4 (SEQ ID No. 4)
; Sequence 4, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
;  APPLICANT: BAUBET, VALERIE
;  APPLICANT:LE MOUELLIC, HERVE
;  APPLICANT:BRULET, PHILIPPE
;  TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
;  TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
;  FILE REFERENCE: 03495-0207-00000
;  CURRENT APPLICATION NUMBER: US/11/149,177
;  CURRENT FILING DATE: 2005-06-10
;  PRIOR APPLICATION NUMBER: 09863901
;  PRIOR FILING DATE: 2001-05-24
;  PRIOR APPLICATION NUMBER: 60/208,314
;  PRIOR FILING DATE: 2000-06-01
;  PRIOR APPLICATION NUMBER: 60/210,526
;  PRIOR FILING DATE: 2000-06-06
;  PRIOR APPLICATION NUMBER: 60/255,111
;  PRIOR FILING DATE: 2000-12-14
;  NUMBER OF SEQ ID NOS: 48
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 4
;  LENGTH: 468
;  TYPE: PRT
;  ORGANISM: Aequorea victoria
US-11-149-177-4

  Query Match             50.5%;  Score 648;  DB 4;  Length 468;
  Best Local Similarity   53.9%;  Pred. No. 7.3e-60;
  Matches  123;  Conservative   40;  Mismatches   61;  Indels    4;  Gaps    2;

Qy          1 MSSGALLFHGKIPYVVEMEGNVDGHTFSIRGKGYGDASVGKVDAQFICTTGDVPVPWSTL 60
              || |  || | :| :||::|:|:|:|| ||: |:| |||: ||:  :|||||| :|||| ||
Db          1 MSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTL 60

Qy         61 VTTLTYGAQCFAKYGPELK--DFYKSCMPDGYVQERTITFEGDGNFKTRAEVTFENGSVY 118
              ||||||| |||::|   :|  ||:|| ||:|||||||| |: |||:|||||| ||  ::
Db         61 VTTLTYGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLV 120

Qy        119 NRVKLNGQGFKKDGHVLGKNLEFNFTPHCLYIWGDQANHGLKSAFKICHEITGSKGDFIV 178
              ||::| |  ||:||::||  ||:|:  | :||  |:  :|:|: ||| | |    |   :
Db        121 NRIELKGIDFKEDGNILGHKLEYNYNSHNVYIMADKQKNGIKANFKIRHNI--EDGSVQL 178

Qy        179 ADHTQMNTPIGGGPVHVPEYHHMSYHVKLSKDVTDHRDNMSLKETVRA 226
              ||| | ||||| ||| :|: |::|    ||||  : ||:| | | | |
Db        179 ADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMVLLEFVTA 226
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RESULT 5
US-11-149-177-5 (SEQ ID No. 5)
; Sequence 5, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
;  APPLICANT: BAUBET, VALERIE
;  APPLICANT:LE MOUELLIC, HERVE
;  APPLICANT:BRULET, PHILIPPE
;  TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
;  TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
;  FILE REFERENCE: 03495-0207-00000
;  CURRENT APPLICATION NUMBER: US/11/149,177
;  CURRENT FILING DATE: 2005-06-10
;  PRIOR APPLICATION NUMBER: 09863901
;  PRIOR FILING DATE: 2001-05-24
;  PRIOR APPLICATION NUMBER: 60/208,314
;  PRIOR FILING DATE: 2000-06-01
;  PRIOR APPLICATION NUMBER: 60/210,526
;  PRIOR FILING DATE: 2000-06-06
;  PRIOR APPLICATION NUMBER: 60/255,111
;  PRIOR FILING DATE: 2000-12-14
;  NUMBER OF SEQ ID NOS: 48
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 5
;  LENGTH: 477
;  TYPE: PRT
;  ORGANISM: Aequorea victoria
US-11-149-177-5

  Query Match            50.5%;  Score 648;  DB 4;  Length 477;
  Best Local Similarity   53.9%;  Pred. No. 7.6e-60;
  Matches  123;  Conservative   40;  Mismatches   61;  Indels    4;  Gaps    2;

Qy          1 MSSGALLFHGKIPYVVEMEGNVDGHTFSIRGKGYGDASVGKVDAQFICTTGDVPVPWSTL 60
              || |  || | :| :||::|:|:|| ||: |:| |||: ||:  :|||||| :|||| ||
Db          1 MSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTL 60

Qy         61 VTTLTYGAQCFAKYGPELK--DFYKSCMPDGYVQERTITFEGDGNFKTRAEVTFENGSVY 118
              ||||||| |||::|   :|  ||:|| ||:|||||||| |: |||:|||||| ||  ::
Db         61 VTTLTYGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLV 120

Qy        119 NRVKLNGQGFKKDGHVLGKNLEFNFTPHCLYIWGDQANHGLKSAFKICHEITGSKGDFIV 178
              ||::| |  ||:||::||  ||:|:  | :||  |:  :|:|: ||| | |    |   :
Db        121 NRIELKGIDFKEDGNILGHKLEYNYNSHNVYIMADKQKNGIKANFKIRHNI--EDGSVQL 178

Qy        179 ADHTQMNTPIGGGPVHVPEYHHMSYHVKLSKDVTDHRDNMSLKETVRA 226
              ||| | ||||| ||| :|: |::|    ||||  : ||:| | | | |
Db        179 ADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMVLLEFVTA 226


RESULT 6
US-11-149-177-6 (SEQ ID No. 6)
; Sequence 6, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
;  APPLICANT: BAUBET, VALERIE
;  APPLICANT:LE MOUELLIC, HERVE
;  APPLICANT:BRULET, PHILIPPE
;  TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
;  TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
;  FILE REFERENCE: 03495-0207-00000
;  CURRENT APPLICATION NUMBER: US/11/149,177
;  CURRENT FILING DATE: 2005-06-10
;  PRIOR APPLICATION NUMBER: 09863901
;  PRIOR FILING DATE: 2001-05-24
;  PRIOR APPLICATION NUMBER: 60/208,314
;  PRIOR FILING DATE: 2000-06-01
;  PRIOR APPLICATION NUMBER: 60/210,526
;  PRIOR FILING DATE: 2000-06-06
;  PRIOR APPLICATION NUMBER: 60/255,111
;  PRIOR FILING DATE: 2000-12-14
;  NUMBER OF SEQ ID NOS: 48
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 6
;  LENGTH: 906
;  TYPE: PRT
;  ORGANISM: Aequorea victoria
US-11-149-177-6

  Query Match            50.5%;  Score 648;  DB 4;  Length 906;
  Best Local Similarity   53.9%;  Pred. No. 2e-59;
  Matches  123;  Conservative   40;  Mismatches   61;  Indels    4;  Gaps    2;
```

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Qy          1 MSSGALLFHGKIPYVVEMEGNVDGHTFSIRGKGYGDASVGKVDAQFICTTGDVPVPWSTL 60
              || |  || | :| :||::|:|:|| ||: |:| |||: ||:  :|||||| :|||| ||
Db        430 MSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPTL 489

Qy         61 VTTLTYGAQCFAKYGPELK--DFYKSCMPDGYVQERTITFEGDGNFKTRAEVTFENGSVY 118
              ||||||| |||::|   :|  ||:|| ||:|||||||| |: |||:|||||| ||  ::
Db        490 VTTLTYGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLV 549

Qy        119 NRVKLNGQGFKKDGHVLGKNLEFNFTPHCLYIWGDQANHGLKSAFKICHEITGSKGDFIV 178
              ||::| |  ||:||::||  ||:|:  | :||  |:  :|:|: ||| | |    |   :
Db        550 NRIELKGIDFKEDGNILGHKLEYNYNSHNVYIMADKQKNGIKANFKIRHNI--EDGSVQL 607

Qy        179 ADHTQMNTPIGGGPVHVPEYHHMSYHVKLSKDVTDHRDNMSLKETVRA 226
              ||| | ||||| ||| :|: |::|    ||||  : ||:| | | | |
Db        608 ADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMVLLEFVTA 655
```

(B) Alignment of SEQ ID No. 9 of instant application with SEQ ID Nos 7-12 of Baubet et al.

```
RESULT 1
US-11-149-177-9 (SEQ ID No. 9)
; Sequence 9, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
;  APPLICANT: BAUBET, VALERIE
;  APPLICANT:LE MOUELLIC, HERVE
;  APPLICANT:BRULET, PHILIPPE
;  TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
;  TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
;  FILE REFERENCE: 03495-0207-00000
;  CURRENT APPLICATION NUMBER: US/11/149,177
;  CURRENT FILING DATE: 2005-06-10
;  PRIOR APPLICATION NUMBER: 09863901
;  PRIOR FILING DATE: 2001-05-24
;  PRIOR APPLICATION NUMBER: 60/208,314
;  PRIOR FILING DATE: 2000-06-01
;  PRIOR APPLICATION NUMBER: 60/210,526
;  PRIOR FILING DATE: 2000-06-06
;  PRIOR APPLICATION NUMBER: 60/255,111
;  PRIOR FILING DATE: 2000-12-14
;  NUMBER OF SEQ ID NOS: 48
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 9
;  LENGTH: 1350
;  TYPE: DNA
;  ORGANISM: Aequorea victoria
US-11-149-177-9

  Query Match             47.1%;  Score 332.2;  DB 3;  Length 1350;
  Best Local Similarity   70.1%;  Pred. No. 1.2e-73;
  Matches  480;  Conservative    0;  Mismatches  193;  Indels   12;  Gaps    2;

Qy          1 ATGAGCAGCGGCGCCCTGCTGTTCCACGGCAAGATCCCCTACGTGGTGGAGATGGAGGGC 60
              |||||||  ||||    |||||||  |||   | | |||  | |||| ||| |||| |||
Db          1 ATGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGC 60

Qy         61 AATGTGGATGGCCACACCTTCAGCATCCGCGGCAAGGGCTACGGCGATGCCAGCGTGGGC 120
               | ||  | |||||||  |||||| |   |||| ||||| | |||||||||| |   |||
Db         61 GACGTAAACGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGC 120

Qy        121 AAGGTGGATGCCCAGTTCATCTGCACCACCGGCGATGTGCCCGTGCCCTGGAGCACCCTG 180
              ||| ||       |||||||||||||||||||| |  |||||||||||||  ||||||
Db        121 AAGCTGACCCTGAAGTTCATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTC 180

Qy        181 GTGACCACCCTGACCTACGGCGCCCAGTGCTTCGCCAAGTACGGCCCCGAGCTGAAG--- 237
              ||||||||||||||||||||  |||||||||  |   |||  |  | |  |||||
Db        181 GTGACCACCCTGACCTACGGCGTGCAGTGCTTCAGCCGCTACCCCGACCACATGAAGCAG 240

Qy        238 ---GATTTCTACAAGAGCTGCATGCCCGATGGCTACGTGCAGGAGCGCACCATCACCTTC 294
                 || |||| ||||  |  |||||||| |||||||| ||||||||||||||  ||||
Db        241 CACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTC 300

Qy        295 GAGGGCGATGGCAATTTCAAGACCCGCGCCGAGGTGACCTTCGAGAATGGCAGCGTGTAC 354
               ||| ||| ||||| | |||||||||||||||||||  ||||||   | || | ||
Db        301 AAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTG 360

Qy        355 AATCGCGTGAAGCTGAATGGCCAGGGCTTCAAGAAGGATGGCCACGTGCTGGGCAAGAAT 414
              || ||| |  ||||||| |||   | ||||||| |||| ||| || | |||||  | ||
Db        361 AACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAG 420
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Qy        415 CTGGAGTTCAATTTCACCCCCCACTGCCTGTACATCTGGGGCGATCAGGCCAATCACGGC 474
              ||||||| ||| | || |  ||||  | | || |||  || |||  ||   ||  |||||
Db        421 CTGGAGTACAACTACAACAGCCACAACGTCTATATCATGGCCGACAAGCAGAAGAACGGC 480

Qy        475 CTGAAGAGCGCCTTCAAGATCTGCCACGAGATCACCGGCAGCAAGGGCGATTTCATCGTG 534
               | |||  |  |||||||||| ||||| | |||   | | |||  |   |  ||
Db        481 ATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCAGCGTGCAGCTC------ 534

Qy        535 GCCGATCACACCCAGATGAATACCCCCATCGGCGGCGGCCCCGTGCACGTGCCCGAGTAC 594
              ||||| |||  ||||  ||| |||||||||||| ||||||||||   |||||||  ||
Db        535 GCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAAC 594

Qy        595 CACCACATGAGCTACCACGTGAAGCTGAGCAAGGATGTGACCGATCACCGCGATAATATG 654
              ||| || |||||  |||       |||||||| ||    | |||  | |||||| | |||
Db        595 CACTACCTGAGCACCCAGTCCGCCCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATG 654

Qy        655 AGCCTGAAGGAGACCGTGCGCGCCG 679
                ||||  ||||  ||||  |||||
Db        655 GTCCTGCTGGAGTTCGTGACCGCCG 679
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RESULT 2
US-11-149-177-10 **(SEQ ID No. 10)**
; Sequence 10, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
; APPLICANT: BAUBET, VALERIE
; APPLICANT:LE MOUELLIC, HERVE
; APPLICANT:BRULET, PHILIPPE
; TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
; TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
; FILE REFERENCE: 03495-0207-00000
; CURRENT APPLICATION NUMBER: US/11/149,177
; CURRENT FILING DATE: 2005-06-10
; PRIOR APPLICATION NUMBER: 09863901
; PRIOR FILING DATE: 2001-05-24
; PRIOR APPLICATION NUMBER: 60/208,314
; PRIOR FILING DATE: 2000-06-01
; PRIOR APPLICATION NUMBER: 60/210,526
; PRIOR FILING DATE: 2000-06-06
; PRIOR APPLICATION NUMBER: 60/255,111
; PRIOR FILING DATE: 2000-12-14
; NUMBER OF SEQ ID NOS: 48
; SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 10
; LENGTH: 1404
; TYPE: DNA
; ORGANISM: Aequorea victoria
US-11-149-177-10

Query Match 47.1%; Score 332.2; DB 3; Length 1404;
Best Local Similarity 70.1%; Pred. No. 1.2e-73;
Matches 480; Conservative 0; Mismatches 193; Indels 12; Gaps 2;

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Qy          1 ATGAGCAGCGGCGCCCTGCTGTTCCACGGCAAGATCCCCTACGTGGTGGAGATGGAGGGC 60
              |||||||  ||||    |||||||  |||   | | |||  | |||| ||| |||| |||
Db          1 ATGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGC 60

Qy         61 AATGTGGATGGCCACACCTTCAGCATCCGCGGCAAGGGCTACGGCGATGCCAGCGTGGGC 120
               | ||  | |||||||  |||||| |   |||| ||||| | |||||||||| |   |||
Db         61 GACGTAAACGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGC 120

Qy        121 AAGGTGGATGCCCAGTTCATCTGCACCACCGGCGATGTGCCCGTGCCCTGGAGCACCCTG 180
              ||| ||       |||||||||||||||||||| |  |||||||||||||  ||||||
Db        121 AAGCTGACCCTGAAGTTCATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTC 180

Qy        181 GTGACCACCCTGACCTACGGCGCCCAGTGCTTCGCCAAGTACGGCCCCGAGCTGAAG--- 237
              |||||||||||||||||||  |||||||||  |   |||  |  | |  |||||
Db        181 GTGACCACCCTGACCTACGGCGTGCAGTGCTTCAGCCGCTACCCCGACCACATGAAGCAG 240

Qy        238 ---GATTTCTACAAGAGCTGCATGCCCGATGGCTACGTGCAGGAGCGCACCATCACCTTC 294
                 || |||| ||||  |  ||||||||| |||||||| ||||||||||||||  ||||
Db        241 CACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTC 300

Qy        295 GAGGGCGATGGCAATTTCAAGACCCGCGCCGAGGTGACCTTCGAGAATGGCAGCGTGTAC 354
               ||| ||| ||||| | |||||||||||||||||||  ||||||   | || | ||
Db        301 AAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTG 360

Qy        355 AATCGCGTGAAGCTGAATGGCCAGGGCTTCAAGAAGGATGGCCACGTGCTGGGCAAGAAT 414
              || ||| |  ||||||| |||   | ||||||| |||| ||| || | |||||  | ||
Db        361 AACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAG 420

Qy        415 CTGGAGTTCAATTTCACCCCCCACTGCCTGTACATCTGGGGCGATCAGGCCAATCACGGC 474
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              ||||||| ||| | || |  ||||  | | || |||  || |||  ||   ||  |||||
Db        421 CTGGAGTACAACTACAACAGCCACAACGTCTATATCATGGCCGACAAGCAGAAGAACGGC 480

Qy        475 CTGAAGAGCGCCTTCAAGATCTGCCACGAGATCACCGGCAGCAAGGGCGATTTCATCGTG 534
               | |||  |  |||||||||| ||||| | |||   | | |||  |   |  ||
Db        481 ATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCAGCGTGCAGCTC------ 534

Qy        535 GCCGATCACACCCAGATGAATACCCCCATCGGCGGCGGCCCCGTGCACGTGCCCGAGTAC 594
              ||||| |||  ||||  ||| |||||||||||| ||||||||||   |||||||  ||
Db        535 GCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAAC 594

Qy        595 CACCACATGAGCTACCACGTGAAGCTGAGCAAGGATGTGACCGATCACCGCGATAATATG 654
              ||| || |||||  |||       |||||||| ||    | |||  | |||||| | |||
Db        595 CACTACCTGAGCACCCAGTCCGCCCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATG 654

Qy        655 AGCCTGAAGGAGACCGTGCGCGCCG 679
                ||||  ||||  ||||  |||||
Db        655 GTCCTGCTGGAGTTCGTGACCGCCG 679


RESULT 3
US-11-149-177-11 (SEQ ID No. 11)
; Sequence 11, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
;  APPLICANT: BAUBET, VALERIE
;  APPLICANT:LE MOUELLIC, HERVE
;  APPLICANT:BRULET, PHILIPPE
;  TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
;  TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
;  FILE REFERENCE: 03495-0207-00000
;  CURRENT APPLICATION NUMBER: US/11/149,177
;  CURRENT FILING DATE: 2005-06-10
;  PRIOR APPLICATION NUMBER: 09863901
;  PRIOR FILING DATE: 2001-05-24
;  PRIOR APPLICATION NUMBER: 60/208,314
;  PRIOR FILING DATE: 2000-06-01
;  PRIOR APPLICATION NUMBER: 60/210,526
;  PRIOR FILING DATE: 2000-06-06
;  PRIOR APPLICATION NUMBER: 60/255,111
;  PRIOR FILING DATE: 2000-12-14
;  NUMBER OF SEQ ID NOS: 48
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 11
;  LENGTH: 1431
;  TYPE: DNA
;  ORGANISM: Aequorea victoria
US-11-149-177-11

  Query Match             47.1%;  Score 332.2;  DB 3;  Length 1431;
  Best Local Similarity   70.1%;  Pred. No. 1.2e-73;
  Matches  480;  Conservative    0;  Mismatches  193;  Indels   12;  Gaps    2;

Qy          1 ATGAGCAGCGGCGCCCTGCTGTTCCACGGCAAGATCCCCTACGTGGTGGAGATGGAGGGC 60
              |||||||  ||||    |||||||  |||   | | |||  | |||| ||| |||| |||
Db          1 ATGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGC 60

Qy         61 AATGTGGATGGCCACACCTTCAGCATCCGCGGCAAGGGCTACGGCGATGCCAGCGTGGGC 120
               | ||  | |||||||  |||||| |   |||| ||||| | |||||||||| |   |||
Db         61 GACGTAAACGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGC 120

Qy        121 AAGGTGGATGCCCAGTTCATCTGCACCACCGGCGATGTGCCCGTGCCCTGGAGCACCCTG 180
              ||| ||       |||||||||||||||||||| |  |||||||||||||  ||||||
Db        121 AAGCTGACCCTGAAGTTCATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTC 180

Qy        181 GTGACCACCCTGACCTACGGCGCCCAGTGCTTCGCCAAGTACGGCCCCGAGCTGAAG--- 237
              ||||||||||||||||||||||  |||||||||  |   |||  |  | |  |||||
Db        181 GTGACCACCCTGACCTACGGCGTGCAGTGCTTCAGCCGCTACCCCGACCACATGAAGCAG 240

Qy        238 ---GATTTCTACAAGAGCTGCATGCCCGATGGCTACGTGCAGGAGCGCACCATCACCTTC 294
                 || |||| ||||  |  ||||||||| ||||||| ||||||||||||||  ||||
Db        241 CACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTC 300

Qy        295 GAGGGCGATGGCAATTTCAAGACCCGCGCCGAGGTGACCTTCGAGAATGGCAGCGTGTAC 354
               ||| ||| ||||| | |||||||||||||||||||  ||||||   | || | ||
Db        301 AAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTG 360

Qy        355 AATCGCGTGAAGCTGAATGGCCAGGGCTTCAAGAAGGATGGCCACGTGCTGGGCAAGAAT 414
              || ||| |  ||||||| |||   | ||||||| |||| ||| || | |||||  | ||
Db        361 AACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAG 420

Qy        415 CTGGAGTTCAATTTCACCCCCCACTGCCTGTACATCTGGGGCGATCAGGCCAATCACGGC 474
              ||||||| ||| | || |  ||||  | | || |||  || |||  ||   ||  |||||
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Db        421 CTGGAGTACAACTACAACAGCCACAACGTCTATATCATGGCCGACAAGCAGAAGAACGGC 480

Qy        475 CTGAAGAGCGCCTTCAAGATCTGCCACGAGATCACCGGCAGCAAGGGCGATTTCATCGTG 534
              | |||  |  |||||||||| ||||| | |||   | | |||  |   |  ||
Db        481 ATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCAGCGTGCAGCTC------ 534

Qy        535 GCCGATCACACCCAGATGAATACCCCCATCGGCGGCGGCCCCGTGCACGTGCCCGAGTAC 594
              ||||| |||  ||||  ||| |||||||||||| ||||||||||   |||||||  ||
Db        535 GCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAAC 594

Qy        595 CACCACATGAGCTACCACGTGAAGCTGAGCAAGGATGTGACCGATCACCGCGATAATATG 654
              ||| || |||||  |||       |||||||| ||    | |||  | |||||| | |||
Db        595 CACTACCTGAGCACCCAGTCCGCCCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATG 654

Qy        655 AGCCTGAAGGAGACCGTGCGCGCCG 679
                ||||  ||||  ||||  |||||
Db        655 GTCCTGCTGGAGTTCGTGACCGCCG 679


RESULT 4
US-11-149-177-8 (SEQ ID No. 8)
; Sequence 8, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
;  APPLICANT: BAUBET, VALERIE
;  APPLICANT:LE MOUELLIC, HERVE
;  APPLICANT:BRULET, PHILIPPE
;  TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
;  TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
;  FILE REFERENCE: 03495-0207-00000
;  CURRENT APPLICATION NUMBER: US/11/149,177
;  CURRENT FILING DATE: 2005-06-10
;  PRIOR APPLICATION NUMBER: 09863901
;  PRIOR FILING DATE: 2001-05-24
;  PRIOR APPLICATION NUMBER: 60/208,314
;  PRIOR FILING DATE: 2000-06-01
;  PRIOR APPLICATION NUMBER: 60/210,526
;  PRIOR FILING DATE: 2000-06-06
;  PRIOR APPLICATION NUMBER: 60/255,111
;  PRIOR FILING DATE: 2000-12-14
;  NUMBER OF SEQ ID NOS: 48
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 8
;  LENGTH: 2673
;  TYPE: DNA
;  ORGANISM: Aequorea victoria
US-11-149-177-8

  Query Match             47.1%;  Score 332.2;  DB 3;  Length 2673;
  Best Local Similarity   70.1%;  Pred. No. 1.3e-73;
  Matches  480;  Conservative    0;  Mismatches  193;  Indels   12;  Gaps    2;

Qy          1 ATGAGCAGCGGCGCCCTGCTGTTCCACGGCAAGATCCCCTACGTGGTGGAGATGGAGGGC 60
              |||||||  ||||    |||||||  |||   | | |||  | |||| ||| |||| |||
Db          1 ATGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGC 60

Qy         61 AATGTGGATGGCCACACCTTCAGCATCCGCGGCAAGGGCTACGGCGATGCCAGCGTGGGC 120
               | ||  | |||||||  |||||| |   |||| ||||| | |||||||||| |   |||
Db         61 GACGTAAACGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGC 120

Qy        121 AAGGTGGATGCCCAGTTCATCTGCACCACCGGCGATGTGCCCGTGCCCTGGAGCACCCTG 180
              ||| ||       |||||||||||||||||||| |  |||||||||||||  ||||||
Db        121 AAGCTGACCCTGAAGTTCATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTC 180

Qy        181 GTGACCACCCTGACCTACGGCGCCCAGTGCTTCGCCAAGTACGGCCCCGAGCTGAAG--- 237
              ||||||||||||||||||||  |||||||||  |   |||  |  | |  |||||
Db        181 GTGACCACCCTGACCTACGGCGTGCAGTGCTTCAGCCGCTACCCCGACCACATGAAGCAG 240

Qy        238 ---GATTTCTACAAGAGCTGCATGCCCGATGGCTACGTGCAGGAGCGCACCATCACCTTC 294
                 || |||| ||||  |  |||||||| |||||||| ||||||||||||||  ||||
Db        241 CACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTC 300

Qy        295 GAGGGCGATGGCAATTTCAAGACCCGCGCCCGAGGTGACCTTCGAGAATGGCAGCGTGTAC 354
               ||| ||| ||||| | ||||||||||||||||||||  ||||||   | || | ||
Db        301 AAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTG 360

Qy        355 AATCGCGTGAAGCTGAATGGCCAGGGCTTCAAGAAGGATGGCCACGTGCTGGGCAAGAAT 414
              || ||| |  ||||||| |||   | ||||||| |||| ||| || | |||||  | ||
Db        361 AACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAG 420

Qy        415 CTGGAGTTCAATTTCACCCCCCACTGCCTGTACATCTGGGGCGATCAGGCCAATCACGGC 474
              ||||||| ||| | || |  ||||  | | || |||  || |||  ||   ||  |||||
Db        421 CTGGAGTACAACTACAACAGCCACAACGTCTATATCATGGCCGACAAGCAGAAGAACGGC 480
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Qy        475 CTGAAGAGCGCCTTCAAGATCTGCCACGAGATCACCGGCAGCAAGGGCGATTTCATCGTG 534
              | |||  |  |||||||||| ||||| | |||   | | |||  |   |  ||
Db        481 ATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCAGCGTGCAGCTC------ 534

Qy        535 GCCGATCACACCCAGATGAATACCCCCATCGGCGGCGGCCCCGTGCACGTGCCCGAGTAC 594
              ||||| |||  ||||  ||| |||||||||||| ||||||||||   |||||||  ||
Db        535 GCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAAC 594

Qy        595 CACCACATGAGCTACCACGTGAAGCTGAGCAAGGATGTGACCGATCACCGCGATAATATG 654
              ||| || |||||  |||       |||||||| ||    | |||  | |||||| | |||
Db        595 CACTACCTGAGCACCCAGTCCGCCCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATG 654

Qy        655 AGCCTGAAGGAGACCGTGCGCGCCG 679
                ||||  ||||  ||||  |||||
Db        655 GTCCTGCTGGAGTTCGTGACCGCCG 679


RESULT 5
US-11-149-177-12 (SEQ ID No. 12)
; Sequence 12, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
;  APPLICANT: BAUBET, VALERIE
;  APPLICANT:LE MOUELLIC, HERVE
;  APPLICANT:BRULET, PHILIPPE
;  TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
;  TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
;  FILE REFERENCE: 03495-0207-00000
;  CURRENT APPLICATION NUMBER: US/11/149,177
;  CURRENT FILING DATE: 2005-06-10
;  PRIOR APPLICATION NUMBER: 09863901
;  PRIOR FILING DATE: 2001-05-24
;  PRIOR APPLICATION NUMBER: 60/208,314
;  PRIOR FILING DATE: 2000-06-01
;  PRIOR APPLICATION NUMBER: 60/210,526
;  PRIOR FILING DATE: 2000-06-06
;  PRIOR APPLICATION NUMBER: 60/255,111
;  PRIOR FILING DATE: 2000-12-14
;  NUMBER OF SEQ ID NOS: 48
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 12
;  LENGTH: 2718
;  TYPE: DNA
;  ORGANISM: Aequorea victoria
US-11-149-177-12

  Query Match             47.1%;  Score 332.2;  DB 3;  Length 2718;
  Best Local Similarity   70.1%;  Pred. No. 1.3e-73;
  Matches  480;  Conservative    0;  Mismatches  193;  Indels   12;  Gaps    2;

Qy          1 ATGAGCAGCGGCGCCCTGCTGTTCCACGGCAAGATCCCCTACGTGGTGGAGATGGAGGGC 60
              |||||||  ||||    |||||||  |||   | | |||  | |||| ||| |||| |||
Db       1288 ATGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGC 1347

Qy         61 AATGTGGATGGCCACACCTTCAGCATCCGCGGCAAGGGCTACGGCGATGCCAGCGTGGGC 120
               | ||  | |||||||  |||||| |   |||| ||||| | |||||||||| |   |||
Db       1348 GACGTAAACGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGC 1407

Qy        121 AAGGTGGATGCCCAGTTCATCTGCACCACCGGCGATGTGCCCGTGCCCTGGAGCACCCTG 180
              ||| ||       |||||||||||||||||||| |  |||||||||||||  ||||||
Db       1408 AAGCTGACCCTGAAGTTCATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTC 1467

Qy        181 GTGACCACCCTGACCTACGGCGCCCAGTGCTTCGCCAAGTACGGCCCCGAGCTGAAG--- 237
              ||||||||||||||||||||  |||||||||  |   |||  |  | |  |||||
Db       1468 GTGACCACCCTGACCTACGGCGTGCAGTGCTTCAGCCGCTACCCCGACCACATGAAGCAG 1527

Qy        238 ---GATTTCTACAAGAGCTGCATGCCCGATGGCTACGTGCAGGAGCGCACCATCACCTTC 294
                 || |||| ||||  |  ||||||||| |||||||| ||||||||||||||  ||||
Db       1528 CACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTC 1587

Qy        295 GAGGGCGATGGCAATTTCAAGACCCGCGCCGAGGTGACCTTCGAGAATGGCAGCGTGTAC 354
               ||| ||| ||||| | |||||||||||||||||||  ||||||   | || | ||
Db       1588 AAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTG 1647

Qy        355 AATCGCGTGAAGCTGAATGGCCAGGGCTTCAAGAAGGATGGCCACGTGCTGGGCAAGAAT 414
              || ||| |  ||||||| |||   | ||||||| |||| ||| || | |||||  | ||
Db       1648 AACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAG 1707

Qy        415 CTGGAGTTCAATTTCACCCCCCACTGCCTGTACATCTGGGGCGATCAGGCCAATCACGGC 474
              ||||||| ||| | || |  ||||  | | || |||  || |||  ||   ||  |||||
Db       1708 CTGGAGTACAACTACAACAGCCACAACGTCTATATCATGGCCGACAAGCAGAAGAACGGC 1767
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Qy        475 CTGAAGAGCGCCTTCAAGATCTGCCACGAGATCACCGGCAGCAAGGGCGATTTCATCGTG 534
              | |||  |  |||||||||| ||||| | |||   | | |||  |   |  ||
Db       1768 ATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCAGCGTGCAGCTC------ 1821

Qy        535 GCCGATCACACCCAGATGAATACCCCCATCGGCGGCGGCCCCGTGCACGTGCCCGAGTAC 594
              ||||| |||  ||||  ||| ||||||||||||| ||||||||||   |||||||  ||
Db       1822 GCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAAC 1881

Qy        595 CACCACATGAGCTACCACGTGAAGCTGAGCAAGGATGTGACCGATCACCGCGATAATATG 654
              ||| || |||||  |||       |||||||| ||    | |||  | |||||| | |||
Db       1882 CACTACCTGAGCACCCAGTCCGCCCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATG 1941

Qy        655 AGCCTGAAGGAGACCGTGCGCGCCG 679
                ||||  ||||  ||||  |||||
Db       1942 GTCCTGCTGGAGTTCGTGACCGCCG 1966
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RESULT 6
US-11-149-177-7 **(SEQ ID No. 7)**
; Sequence 7, Application US/11149177
; Publication No. US20080213879A1
; GENERAL INFORMATION
; APPLICANT: BAUBET, VALERIE
; APPLICANT:LE MOUELLIC, HERVE
; APPLICANT:BRULET, PHILIPPE
; TITLE OF INVENTION: CHIMERIC GFP-AEQUORIN AS BIOLUMINESCENT Ca++ REPORTERS
; TITLE OF INVENTION:AT THE SINGLE CELL LEVEL
; FILE REFERENCE: 03495-0207-00000
; CURRENT APPLICATION NUMBER: US/11/149,177
; CURRENT FILING DATE: 2005-06-10
; PRIOR APPLICATION NUMBER: 09863901
; PRIOR FILING DATE: 2001-05-24
; PRIOR APPLICATION NUMBER: 60/208,314
; PRIOR FILING DATE: 2000-06-01
; PRIOR APPLICATION NUMBER: 60/210,526
; PRIOR FILING DATE: 2000-06-06
; PRIOR APPLICATION NUMBER: 60/255,111
; PRIOR FILING DATE: 2000-12-14
; NUMBER OF SEQ ID NOS: 48
; SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 7
; LENGTH: 3973
; TYPE: DNA
; ORGANISM: Aequorea victoria
US-11-149-177-7

Query Match 47.1%; Score 332.2; DB 3; Length 3973;
Best Local Similarity 70.1%; Pred. No. 1.3e-73;
Matches 480; Conservative 0; Mismatches 193; Indels 12; Gaps 2;

```
Qy          1 ATGAGCAGCGGCGCCCTGCTGTTCCACGGCAAGATCCCCTACGTGGTGGAGATGGAGGGC 60
              |||||||  ||||    |||||||  |||   | | |||  | |||| ||| |||| |||
Db          1 ATGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGC 60

Qy         61 AATGTGGATGGCCACACCTTCAGCATCCGCGGCAAGGGCTACGGCGATGCCAGCGTGGGC 120
               | ||  | |||||||  |||||| |   |||| ||||| | |||||||||| |   |||
Db         61 GACGTAAACGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGC 120

Qy        121 AAGGTGGATGCCCAGTTCATCTGCACCACCGGCGATGTGCCCGTGCCCTGGAGCACCCTG 180
              ||| ||       |||||||||||||||||||| |  ||||||||||||||  ||||||
Db        121 AAGCTGACCCTGAAGTTCATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTC 180

Qy        181 GTGACCACCCTGACCTACGGCGCCCAGTGCTTCGCCAAGTACGGCCCCGAGCTGAAG--- 237
              ||||||||||||||||||||  |||||||||  |   |||  |  | |  |||||
Db        181 GTGACCACCCTGACCTACGGCGTGCAGTGCTTCAGCCGCTACCCCGACCACATGAAGCAG 240

Qy        238 ---GATTTCTACAAGAGCTGCATGCCCGATGGCTACGTGCAGGAGCGCACCATCACCTTC 294
                 || |||| ||||  |  |||||||| |||||||| ||||||||||||||  ||||
Db        241 CACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTC 300

Qy        295 GAGGGCGATGGCAATTTCAAGACCCGCGCCGAGGTGACCTTCGAGAATGGCAGCGTGTAC 354
              |||  ||| ||||| | ||||||||||||||||||||  ||||||   | || | ||
Db        301 AAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTG 360

Qy        355 AATCGCGTGAAGCTGAATGGCCAGGGCTTCAAGAAGGATGGCCACGTGCTGGGCAAGAAT 414
              || ||| |  ||||||| |||   | ||||||| |||| ||| || | |||||  | ||
Db        361 AACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAG 420

Qy        415 CTGGAGTTCAATTTCACCCCCCACTGCCTGTACATCTGGGGCGATCAGGCCAATCACGGC 474
              ||||||| ||| | || |  ||||  | | || |||  || |||  ||   ||  |||||
Db        421 CTGGAGTACAACTACAACAGCCACAACGTCTATATCATGGCCGACAAGCAGAAGAACGGC 480

Qy        475 CTGAAGAGCGCCTTCAAGATCTGCCACGAGATCACCGGCAGCAAGGGCGATTTCATCGTG 534
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            | |||  |  |||||||||| ||||| | |||   | | |||  |   |  ||
Db        481 ATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCAGCGTGCAGCTC------ 534

Qy        535 GCCGATCACACCCAGATGAATACCCCCATCGGCGGCGGCCCCGTGCACGTGCCCGAGTAC 594
              ||||| |||  ||||  ||| |||||||||||| ||||||||||   |||||||  ||
Db        535 GCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAAC 594

Qy        595 CACCACATGAGCTACCACGTGAAGCTGAGCAAGGATGTGACCGATCACCGCGATAATATG 654
              ||| || |||||  |||       |||||||| ||    | |||  | |||||| | |||
Db        595 CACTACCTGAGCACCCAGTCCGCCCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATG 654

Qy        655 AGCCTGAAGGAGACCGTGCGCGCCG 679
                |||| |||| |||| |||||
Db        655 GTCCTGCTGGAGTTCGTGACCGCCG 679
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Thus, Baubet et al. (US 2008/0213879) clearly anticipates claims 1, 5-8, 13, 17, and 27-30 of instant application.

6. Claims 1, 5-8, 13, 17, and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Baubet et al. (PCT/EP01/07057, WO 2001/092300, filed on 06/01/2001).

The following claim interpretations are applied in this rejection.

(i) Claim 1 reads as follows: An isolated nucleic acid molecule comprising nucleotide sequences, which encodes a fluorescent protein having at least 85% identity with an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, **10**, 12, 14, 16, 18, 20, and 22. Claim 1 reads on any isolated nucleic acid molecule comprising nucleotide sequences, which encodes a fluorescent protein having amino acid sequences that have at least 85% identity of any fragment of SEQ ID No. 10. It is emphasized that the phrase "consisting of SEQ ID NOs: 2, 4, 6, **10**, 12, 14, 16, 18, 20, and 22" is only limiting to one of recited SEQ ID No and does not limit the transitional term "comprising" recited in line 1 of claim 1. In this regard, MPEP 2111.02 states: In determining the scope of applicant's claims directed to "a purified oligonucleotide comprising at least a portion of the nucleotide sequence of SEQ ID NO:1 wherein said portion consists of the nucleotide sequence from … to 2473 of SEQ ID NO:1, and wherein said portion of the nucleotide sequence of SEQ ID NO:1 has promoter activity," the court stated that the use

of "consists" in the body of the claims did not limit the open-ended "comprising" language in the claims (emphases added). *Id.* at 1257, 73 USPQ2d at 1367.

(ii) Claim 13 reads as follows: A nucleic acid molecule having a sequence that is substantially the same as, or identical to a nucleotide sequence of at least 300 residues in length of the nucleic acid molecule according to claim 1. The limitation "at least 300 residues in length of the nucleic acid molecule" reads on those identical sequences that are not necessarily continuous.

(iii) Claim 29 is interpreted as a dependent claim of claim 1, rather than a dependent claim of claim 26, which is cancelled.

With regard to claims 1, 5-8, 13, and 27-30, Baubet et al. teaches a modified bioluminescent system comprising a fluorescent molecule covalently linked with a photoprotein, wherein said link between the two proteins has the function to stabilize the modified bioluminescent system and allowing the transfer of the energy by Chemiluminescence Resonance Energy Transfer (CRET) in a host cell (See abstract and Figures 9-11, Baubet et al. US 2008/0213879). Baubet et al. teaches DNA construct with CMV promoter drive the expression of nucleic acid sequences encoding sequences of mutated GFP, followed by the sequences of Poly A of SV40 (See Figure 1, PCT/EP01/07057, WO 2001/092300, filed on 06/01/2001).

With regard to the limitation "kit" recited in claim 17, Baubet et al. teaches kit for measuring the transfer of energy in vivo or in vitro contains at least one of the polypeptides according to the invention or the polynucleotide according to the invention and the reagents

necessary for visualizing or detecting the said transfer in presence or in absence of a molecule of interest (See paragraph [0021], PCT/EP01/07057, WO 2001/092300, filed on 06/01/2001)

It is noted that Baubet et al. (PCT/EP01/07057, WO 2001/092300, filed on 06/01/2001) discloses the same DNA construct and SEQ ID Numbers as those disclosed in Baubet et al. (Baubet et al., US 2008/0213879). The sequence alignments have been presented in the preceding 102(e) rejection.

Thus, Baubet et al. (PCT/EP01/07057, WO 2001/092300, filed on 06/01/2001) clearly anticipates claims 1, 5-8, 13, 17, and 27-30 of instant application.

Conclusion

7. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the Supervisory Patent Examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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